CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ACTIVE INGREDIENT

O-PHENYLPHENOL* & SODIUM O-PHENYLPHENOL**

*OPP: Chemical code # 448, Tolerance # 129, SB 950 # 090
**SOPP or OPP-Na: Chemical code # 248, Tolerance # 50438, SB 950 # 474

July 29, 1986
Revised: March 30, 1987; August 30, 1989; September 3, 1991; February 19, 1993; April 24, 1996; May 20, 1997; and March 16, 2001

I. DATA GAP STATUS

Chronic rat:	No data gap, possible adverse effects [1]
Chronic dog:	No data gap, no adverse effect
Onco rat:	No data gap, possible adverse effect
Onco mouse:	No data gap, possible adverse effect
Repro rat:	No data gap, possible adverse effect
Terato rabbit:	No data gap, possible adverse effect
Terato rat:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotox:	Not required at this time

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[1] See statement on page 2 by J. Gee

Note: toxicology one-liners are attached; these pages contain summaries only; each individual worksheet may contain additional effects.

** indicates acceptable study
Bold face indicates possible adverse effect

Revised file name: T010316
Revised by Stephen J. Rinkus, 3/16/01

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

Note: These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED CHRONIC-ONCOGENICITY, RODENTS

Note: No individual long-term study in the rat has been evaluated as acceptable due to deficiencies in conduct and/or reporting. There are, however, several long-term studies which have examined a number of toxicological parameters in the rat. There is little doubt that ortho-phenylphenol has been associated with oncogenicity as demonstrated in a number of these studies. The data for chronic effects is somewhat less clear for determining a NOEL for non-oncogenic effects. The study that most closely addresses chronic toxicity is record # 145317 in which there was a one-year sacrifice of 20/sex for controls and the high-dose (8000 ppm for males, 10,000 ppm for the females) and 10/sex/dose for the low (800 ppm) and mid (4000 ppm) dose groups. Although there were deficiencies noted in the review of this study, considering all of the collective data, there is no need for another long-term study in the rat at this time and the data gap is considered filled. (Gee, 4/9/01).

Analytical data in the rat chronic toxicity-oncogenicity study (record 145317) and the rat reproduction study (record 141559) indicate that OPP in acetone-corn-oil-feed mixtures at concentrations of 800 ppm or 200 ppm degrade over the span of 1 to 4 weeks whether stored frozen (-23EC) or at room temperature. A similar degradation was not seen with a concentration of 10,000 ppm. (Rinkus, 5/20/97).

129-245 145317 "Technical Grade ortho-Phenylphenol: A Combined Chronic Toxicity/Oncogenicity Testing Study in the Rat" (Wahle, B.S. and Christenson, W.R.; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS.; laboratory project study ID number 92-272-SC; 2/23/96). o-Phenylphenol (OPP), ≥ 99.5% purity, was administered in the diet at 0 ppm (acetone-corn oil treated feed), 800 ppm, 4,000 ppm and 8,000 ppm (males) or 10,000 ppm (females), initially to 70-80 Fischer 344 rats/sex/treatment level. Interim sacrifices were performed after 1 year using 10 (low- and mid-dose groups) or 20 (control and high-dose groups) rats/sex/treatment level. Twelve rats were replaced after the first month of testing. Six of these involved the high-dose female groups (three for the 1-year sacrifice group and three for the 2-year-sacrifice group); these six appeared to have been replaced because they had exhibited perigenital urine staining or a red ocular discharge. Survival was only affected in the high-dose male group: by week 85, 12 animals bearing urinary bladder cancer were dead or had to be sacrificed due to their moribund condition versus two deaths in the male control group. Decreased bodyweight appeared in the first few weeks of the study for both sexes exposed to ≥ 4000 ppm OPP; continued exposure only slightly affected the relative degree of bodyweight reduction. For the 8000 ppm males and 10,000 ppm females, decreased bodyweight paralleled significant decreases in the feed consumed/rat/day. The clinical observation data indicated the following: hematuria (red blood cells in urine; red stained, perigenital fur) presumably associated with the urinary bladder cancer in the 8000 ppm male group; and possibly polyuria (urine-stained, perigenital fur) in each of the OPP-exposed female groups. Ophthalmological testing at the end of the study found significant increases in the

incidences of uveitis, corneal vascularization and cataract in the 4000 ppm female survivors and of cataracts in the 8000 ppm male survivors. At each testing period, two or more mean corpuscular indices (i.e., MCV, MCH & MCHC) were affected statistically, sometimes involving the mid- and high-dose groups and both sexes. However, the data for hematocrit, rbc concentration and hemoglobin concentration did not indicate that OPP had significantly affected these endpoints. Serum- chemistry changes were seen at multiple testing times and often in both sexes in rats exposed to $\geq$ 800 ppm OPP; these changes included: decreased creatine kinase; decreased lactate dehydrogenase; decreased calcium; increased albumin/decreased globulin; decreased triglycerides; decreased cholesterol; increased urea nitrogen; and decreased total bilirubin. In some instances, the same serum-chemistry change had been seen in the 4-week, range-finding study. Treatment- related urinalysis findings included: increased pH at the high dose in both sexes; decreased protein at the mid and high doses in both sexes; decreased ketones at the low, mid and high doses in the males and at the mid and high doses in the females; decreased specific gravity at the mid and high doses in both sexes; and decreased leukocytes at the low, mid and high doses in the males and at the mid and high doses in the females. The urinalysis findings, taken together with the urine staining of the perigenital fur, suggest that the OPP-treated rats had polyuria. Absolute-organ- weight changes appeared to be related to bodyweight decreases or the occurrence of tumors (leukemia in the spleen [females]; interstitial cell tumor in the testes). Necropsy data indicated the following: urinary bladder masses, consistent with urinary bladder cancer, in the mid- and high- dose male groups; kidney changes, consistent with kidney damage, in the high-dose female group; and red stained ventrums, consistent with hematuria resulting from urinary bladder cancer, in the high-dose male group. Histological findings in the kidneys included increased incidences of cystic tubular dilatation/degeneration at the high dose in both sexes, cortical infarct at the high dose in the females (and possibly the males), mineralization within the tubules of the papillae at the high dose in the females, tubular hyperplasia at the high dose in the females, and acute inflammation at the high dose in the females. Histological findings in the urinary bladder included increased incidences of simple transitional cell hyperplasia at the high dose in both sexes, nodular/papillary transitional cell hyperplasia at the high dose in the males, transitional cell carcinomas at the mid and high doses in the males, and transitional cell papillomas at the high dose in the males. High-dose males also exhibited the following urinary bladder findings in association with urinary-bladder tumors: congestion, hemorrhage, mineralization within the tissues, necrosis and calculi. Histological findings also included increased incidences of an eye syndrome consisting of cataract, retinal degeneration, optic nerve atrophy and optic chiasma atrophy in the mid-dose females, vascular mineralization in the heart in the mid-dose males, and cardiomyopathy in the low- and mid-dose females. The incidence and (or) spread of mononuclear cell leukemia (MCL) appeared to be increased in the 800 ppm males but supplemental information was needed to complete the evaluation. When first reviewed (1/21/97), this study was considered unacceptable pending the submission of supplemental information (detailed in worksheet W145317.835). In response, the Registrant submitted records 168946 and 169048. Based on the former, it is possible that orbital-sinus bleeding of the right eye was involved in the increased incidences of eye lesions in the 4000 ppm female survivors seen at ophthalmology and in the increased incidence of the afore-mentioned eye syndrome in the 4000 ppm female group seen at histology. However, other deficits in various data regarding the eyes and optic nerve need to be resolved before deciding these issues. The supplemental information also indicated that the incidence of MCL-bearing animals was statistically increased ($p<0.01$) in the 800 ppm males that survived to terminal sacrifice. However, given the lack of a similar response in the 4000 ppm males and the known variability in the incidence of MCL in F344 males, there is insufficient evidence to conclude that the increased MCL incidence was treatment-related. Whether the onset or spread of MCL was affected by treatments remains unresolved. **Possible adverse effect: urinary bladder cancer. Noncancer NOEL <**

800 ppm (polyuria [urine-fur staining, urinalysis changes]; serum-chemistry changes; cardiomyopathy). This study is still considered **UNACCEPTABLE**. (Rinkus, 10/5/00).

129-281 168946 This record consists of a 36-page narrative section that provides a response to issues raised in worksheet W145317.835, with the following 7 appendices: Appendix I, worksheet W145317.835; Appendix II, individual urinary-volume data taken on study day 22 of the four-week range-finding toxicity study; Appendix III, historical negative-control data from the conducting laboratory in the areas of clinical chemistry, hematology and urinalysis; Appendix IV, a compilation of Fisher exact tests conducted on the revised clinical-observation data; Appendix V, clinical-observation summary data excluding the data for the replacement rats; Appendix VI, individual clinical-observation data for the one-year-sacrifice and two-year-sacrifice groups, excluding the data for the replacement rats; and Appendix VII which consists of four parts: Part 1 contains responses to issues raised in section VI in worksheet W145317.835 as well as to related issues that were raised elsewhere in that worksheet; Part 2 contains responses to 10 miscellaneous issues that appeared in section IV of worksheet W145317.835; Part 3 contains analyses of the MCL data and of data related to whether OPP had affected the eyes, optic nerves and optic chiasma; and Part 4 contains 38 tables to which references were made in the previous three parts. **Supplemental information, discussed in worksheet w145317.s01**. (Rinkus, 3/16/01).

129-282 169048 This record consists of two parts. First, there is an 8-page section whose purpose was to correct the year appearing on page 10 of record 168946. The second part began with a letter dated May 13, 1999, from Stan Olosky (Bayer) to Karen Fletcher (DPR), indicating that "raw data" were attached, pursuant to discussions that had occurred between representatives of the Registrant and Medical Toxicology staff at a meeting held on February 10, 1998. Pages are not numbered sequentially in this part. There are the following 8 sections (in order of appearance): 1) use of death-rate and prevalence methods to analyze survival-adjusted mononuclear-cell leukemia (MCL) incidence data; also summary statistics regarding the number of tumorous tissues per animal having MCL; 2) summary statistics of absolute organ weights (spleen, liver, lung) from animals with MCL; 3) survival-analysis tables, Kaplan-Meier plots and summary statistical analyses; also individual animal fate data; 4) a summary table of incidence data for 70 endpoints; the endpoints included histology, necropsy, clinical observations and ophthalmology from the one-year-sacrifice and two-year-sacrifice groups; endpoints were selected on the basis of visual examination of the data for a significant difference when compared to controls; following the summary table, there were individual 2x4 (all groups compared) and 2x2 (controls versus a treatment group) contingency tables with summary statistical analyses; 5) individual contingency tables with summary statistical analyses concerning necropsy observations of the ventrum; 6) individual contingency tables with summary statistical analyses concerning several endpoints; 7) individual contingency tables with summary statistical analyses concerning eye-histology endpoints; and 8) tables listing individual data for organ weights (liver, lungs, spleen) for animals that were either found dead or were sacrificed due to their moribund state. **Supplemental information, discussed in worksheet w145317.s01**. (Rinkus, 3/16/01).

****129-058 065929** "Carcinoginicity Testing of Sodium Orthophenylphenate in F-344/DuCrj Rats," (Kogo Hiraga [author], Tokyo Metropolitan Research Laboratory of Public Health, 1983). Sodium o-phenylphenol (OPP-Na), a stated purity of 95.5%, was given in the feed at concentrations of 0, 0.7 and 2% to 50 male rats and at 0, 0.5 and 1% to 50 female rats for 104 weeks in the 106-week study. OPP-Na also was given in the feed at 0, 0.25, 0.7 and 2% to 25 males and at 0, 0.25, 0.5 and 1% to 25 females for 104 weeks in the lifespan study. After dietary exposure to OPP-Na, rats then were fed basal diet for either two more weeks (106-week study) or until death (lifespan

study). Reduced mean bodyweights were observed in the high-dose males and females in the 106-week study and in the high-dose males in the life-span study. Hematuria and early deaths were noted only in the high-dose males and may have resulted from the presence of urinary bladder tumors. These tumors arose in the transitional epithelium of the urinary bladder; some tumors also were induced in the transitional epithelium of the renal pelvis in high-dose males in the the 106-week study. At the high-dose level in both study designs, the incidence of urinary bladder tumors in the males was > 90%. Also, nonneoplastic lesions were seen in the pancreas (females only), the testis and the urinary tract. **NOEL = 224 mg/kg/day as nominal time-weighted average (2500 ppm nominal) (tumors & hyperplasia in the urinary tract of females).** This record was considered originally to be unacceptable as a rat oncogenicity study; upgrading required the submission of data testifying to the stability of OPP-Na in the feed under the storage conditions used in this study (Rinkus & Kishiyama, 6/6/89). These analytical data now have been provided in record 091951; as a result, this study has been reclassified as **ACCEPTABLE** only as a rat oncogenicity study. In terms of chronic toxicity testing, this study remains unacceptable because there are insufficient data in the areas of hematology and ophthalmology. (Rinkus, 4/5/91).

129-058 065931 "Carcinogenicity Testing of Sodium Orthophenylphenate in F 344 Rats," (Fujii, T. and Hiraga, K., J. Saitama Med. School, 12: 277-287, 1985). Partial duplicate of 129-058 065929. Materials and Methods section indicates that "test diets were prepared once per three months," an important point which was not mentioned in 129-058 065929. No worksheet. (Rinkus, 7/13/89).

129-010 004164 "Toxicological Studies of Orthophenylphenol (Dowicide 1)," (Dow, 2/52, published article in J. Pharmacol. Experimental Therapeutics 104: 202-210 (1952), Hodge, H. C. et al.). OPP (>98%) fed in the diet for 2 years at 0, 200, 2000 or 20,000 ppm (0.02. 0.2 or 2.0%); 25/sex/group; **UNACCEPTABLE** (limited data, no analysis of diets, no report on clinical findings or hematology/urinalysis/clinical chemistry, inadequate tissues for histopathology). **Positive for adverse effects to the kidneys ("marked tubular dilation" at the high dose).** NOEL=2000 ppm according to text of article. (Remsen (Gee), 4/2/85).

50438-005 038120 "Molecular Mechanisms Involved in the Toxicity of Ortho- phenylphenol and its Sodium Salt," (Dow, 1981, published in: Chem.-Biol. Interactions 43: 99-119 (1983), Reitz, R.H. et al.). Subchronic study (3 to 90 days) with 2% OPP or 2% SOPP in the diet fed to 30 male rats per group for the purpose of studying the effects on kidney and bladder, specifically; OPP, lot MM09250, 99.6% and SOPP, lot MM09220B, 72% SOPP, 25.6% water and 1.05% NaOH; fed in the diet with sacrifices at days 3, 7, 14, 30, 65 and 90, 5-7 per sacrifice group; OPP decreased the food intake in the first week so severely that seven died apparently from starvation. Beginning day 30 on OPP, focal areas of discoloration in kidney were seen upon necropsy and microscopy showed multiple areas of focal tubular collapse and atrophy of the cortex and days 65 and 90 sacrifices showed "cystic degeneration suggestive of obstructive phenomenon." No bladder lesions related to treatment. With SOPP, beginning day 3, increased mitosis was seen in the bladder epithelium. At subsequent times, the proportion reportedly appeared to decrease but remained above normal. Beginning day 14, thickening of the bladder epithelium was seen and increased with time. Reviewed as **supplemental** to chronic/onco studies. (Gee, 3/30/87).

129-032 035998 "Molecular Mechanisms Involved in the Toxicity of Ortho-phenylphenol and Its Sodium Salt," (Reitz et al.; Dow Chemical Company; HET K-1025-(8); 12/10/81). This appears to be the laboratory report which is the basis for record 038120. It contains some data that did not appear in that publication. **Supplementary information. No worksheet.** (Rinkus, 3/29/91).

129-032 036006 "Biochemical Factors Involved in the Effects of Orthophenylphenol (OPP) and Sodium Orthophenylphenate (SOPP) on the Urinary Tract of Male F344 Rats," (Reitz et al., Toxicol. Appl. Pharmacol., 73: 345-349, 1984). **Supplemental information. No worksheet.** (Rinkus, 3/29/91).

129-032 036005 "Follow Up Studies of the Effects of Orthophenylphenol (Dowicide®1) and Sodium Orthophenylphenol (Dowicide A) on the Urinary Tract of F344 Rats," (Reitz et al.; Dow Chemical Company; HET-K-1025-(11); 3/2/83). Male F344 rats (6/group) were fed one of the following diets for 30 days: 1) a control diet; 2) a diet containing 1.3% OPP; 3) a diet containing 2% SOPP (this is equimolar in OPP to the 1.3% OPP diet); 4) a diet containing 10% NaCl; 5) a diet containing 10% NaCl plus 0.1% NaOH; and 6) a diet containing 1.3% OPP, 10% NaCl and 0.1% NaOH. Histological examinations of the urinary tract indicated that the addition of sodium to the diet did not affect the toxicity of OPP (i.e., it did not make it SOPP-like). The in vitro microsome-binding data and the in vivo macromolecular binding data in this record are the basis for record 036006. **Supplementary information. No worksheet.** (Rinkus, 3/29/91).

129-032 036009 "Induction of Tumors of the Urinary Bladder in F344 Rats by Dietary Administration of o-phenylphenol", (Journal article (1984) published in: Fd. Chem. Toxic. 22: 865-870, Hiraga K. and Fujii, T.). OPP (>98%, lot no. MM01040) was administered in the diet at 1560, 3130, 6250, 12,500, or 25,000 ppm to male F344/DuCrj rats for 91 weeks; these doses are equivalent to 0.25, 0.5, 1, 2, or 4% OPP-Na, doses used in other studies. OPP stated to be stable in the diet as measured by gas chromatography; 20-24 males per group. The mean intakes in the 91-week study for the 6250, 12,500 and 25,000 ppm groups were 269, 531 and 1140 mg/kg/day, respectively. The report also contains information on a 13-week study in male and female rats at the same dose levels of OPP. In the 91-week study, urinary bladder tumors noted in 96% of animals at 12,500 ppm and 17% of animals at 25,000 ppm; transitional cell carcinomas were identified in 87% of animals in the 12,500 ppm group and 50% in the 25,000 ppm group. Proliferative lesions of the urinary bladder were also seen in the 13-week group with 12/12 (100%) of males in 12,500 ppm group but in no other group - half were transitional-cell papillomas and half were transitional-cell hyperplasias. In the 91-week study, calculi were found in 17/24 (71%) of the 12,500 ppm males and in 14/23 (61%) of the high dose group. In addition, nephritic lesions were also increased significantly in the high dose groups in both studies. Survival was adversely effected in the mid- and high-dose groups. The discussion compares these results with those for OPP-Na in rats with good correlation but with the suggestion that OPP-Na may be a more effective carcinogen - the sodium salt is quite alkaline (pH 11.8) when dissolved in water and this is suggested as a possible factor. **UNACCEPTABLE** (missing information and use of males only) with a **positive adverse effect.** (Gee, 5/30/86).

50438-005 038118. Partial duplicate of 036009.

50438-005 038117, 038119, "Induction of Tumors of the Urinary System in F344 Rats by Dietary Administration of Sodium o-phenylphenate", (Report and Journal article (1981) Published in Fd. Cosmet. Toxicol. 19: 303-310, Hiraga and Fujii). Male Fisher rats (F344/DuCrj) were exposed to sodium salt of OPP (lot MM01044, $\geq$ 95% (Dow))at levels of 0, 1250, 2500, 5000, 20,000 or 40,000 ppm in the diet for 91 weeks, one analysis of pellets presented; 21/group; increased incidence of transitional cell carcinomas in urinary bladder, renal pelvis and renal papilla at 10,000 (1/21), 20,000 (20/21) and 40,000 (17/20) ppm. All were transitional cell carcinomas with one exception of a carcinosarcoma in the 20,000 ppm group. Severe pyelonephritis occurred in 19/20 of the high dose group. **UNACCEPTABLE** (use of males only, inadequate number of animals at

risk, missing data). Individual data in 038117. (Gee, 5/30/86).

129-047 050577. Duplicate of 038119.

50438-005 038116. Addendum (letter - no data) to 038117.

129-032 036007 "Promoting Effect of Sodium o-Phenylphenate and o-Phenylphenol on Two-Stage Urinary Bladder Carcinogenesis in Rats", (Nagoya City University Medical School, in: Gann 74: 625-632 (1983) by Fukushima, S., et al). OPP-Na, 97% (Lot no. 04279A) and OPP, 98% (Lot no. ARO1); 2% of diet (actual level was 1.59% OPP-Na in expt. 1 and 1.50% in expt. 2; actual level of OPP was 1.72%); stable for 3 months--conditions not specified; some groups of rats were given 0.01 or 0.05% N-butyl-N-(4-hyroxybutyl)nitrosamine (BBN) in the drinking water for 4 weeks prior to feeding with OPP-Na or OPP for 32 weeks; 30 males per group; OPP-Na had a positive effect both with BBN and alone; OPP was not a promoter. **Supplemental information.** (Pfeifer, 9/4/86 and Gee, 3/9/87).

50438-005 038129. Duplicate of 036007.

129-032 036008 "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans," (IARC Working Group, 3/83, WHO, volume 30). The Working Group concluded that the available data (e.g., record 004164) were inadequate to evaluate the carcinogenicity of OPP in experimental animals but there was "limited evidence" (record 038117/038119) that OPP-Na is carcinogenic to the urinary tract of rats, producing both benign and malignant tumors. The Working Group noted that no data on humans were available. (**Note:** in 1987, IARC [Supplement 7] identified OPP-Na has having "sufficient evidence" that it is carcinogenic in experimental animals; this publication presently is not on file at CDPR). (Rinkus, 9/3/91).

242-051 074911 "Enhancing Effect of Thiabendazole on Urinary Bladder Carcinogenesis Induced by Sodium o-Phenylphenate in F344 Rats" (Fujii et al., Fd. Chem. Toxic. 24: 207-211, 1986). The tumor incidences in males eating a diet containing 1% OPP-Na & 0.2% Thiabendazole for 13 weeks or 65 weeks was 80% in both cases (8/10 and 12/15, respectively). By contrast, in males eating just 1% OPP-Na for either exposure period, no tumors were seen (0/10 and 0/15); and in males just eating 0.2% Thiabendazole for 13 weeks or 65 weeks, the respective tumor incidences were 0% (0/10) and 6.7% (1/15). The tumor incidence in females eating a diet containing 2% OPP-Na & 0.2% Thiabendazole for 65 weeks was 80% (12/15), whereas the respective tumor incidences in females just eating 2% OPP-Na or 0.2% Thiabendazole for 65 weeks were 13% (2/15) and 0% (0/15). These enhanced tumor incidences due to cotreatment with Thiabendazole were statistically significant. This study is also useful for indicating the magnitude of the sex difference in the tumor incidences in rats treated chronically to the same diet concentration of OPP-Na: for 2% diets given for 65 weeks, males and females exhibited 100% (15/15) and 13% (2/15) tumor incidences, respectively. **Supplemental Information.** No worksheet. (Rinkus, 8/30/89).

129-059 065932 This record contains tables (but no text) that were part of the presentation made by the Sponsor**s** at a meeting at CDFA Medical Toxicology Branch on 1/28/88. The tables compare FIFRA requirements for oncogenicity testing in rodents, chronic toxicity testing in two species, teratology testing in two species, and reproduction toxicity testing in rats to the various studies that had been submitted by the Sponsors to fill SB950 data requirements (**note**: most of these studies had been conducted by researchers other than those of the Sponsors, e.g., records

065929, 045322, 065930 & 03813.). **Supplementary information. No worksheet.** (Rinkus, 3/29/91).

129-166 113826 This record contains two letters. The one dated 3/31/92 discusses the status of the following SB 950 data requirements: chronic toxicity in rats, oncogenicity in mice, reproduction in rats, and teratogenicity in rabbits. The other letter is discussed under this record number in the section "Teratology, Rabbit." **Supplemental information. No worksheet.** (Rinkus, 8/4/92).

129-166 113774 This record is a protocol for a dietary combined chronic toxicity-oncogenicity study using B6C3F1 mice. The test material appears to be o-phenylphenol (as opposed to its sodium salt). **Supplemental information. No worksheet.** (Rinkus, 8/4/92).

ANALYTICAL STUDIES, IN SUPPORT OF CHRONIC STUDIES

Note: With the submission of record 091951, the matter that was discussed in the rebuttal dated 8/30/89 (R890830), regarding inadequate analytical data to support the chronic study in rats (record 065929), can be considered resolved. (Rinkus, 4/5/91).

129-140 091951 "Stability of Ortho-Phenylphenol (OPP) and Sodium Salt of Ortho-Phenylphenol (OPP-Na) in Rodent Chow Used in Japanese Toxicity Studies," (Sowle et al.; The Dow Chemical Company; Laboratory Project Study ID T2.02-195-000-002; 12/18/90). OPP (lot # MM890315) and OPP-Na (lot # 890831), both technical grades and both having ≥ 99% purity, were tested separately for their stability in rodent chow. The chow was obtained from Japan (Clea Diet CE-2, Clea Japan, Inc., Tokyo) and the preparation methodology and storage conditions that were used simulated those used in the chronic studies in rats conducted by Japanese researchers at the Tokyo Metropolitan Research Laboratory of Public Health (e.g., record 065929). This stability study was performed in response to concerns raised by CDFA (R890830) that the Sponsor was using these chronic studies in rats to fill certain SB950 data requirements but the analytical studies to support these studies (records 068363, 068361 & 068362) were inadequate and there was even possible evidence that the test material was unstable in the diet (record 072405). The stability study of both forms of OPP was conducted as follows. Test material was ground to create a fine powder and then combined with pulverized chow to produce eventually diets containing 0% (control), 0.25%, 0.50%, 0.70%, 1.00% and 2.00% (w/w) (**note:** a total of 12 test diets). The powder diets were shipped to Purina Mills in Richmond, Indiana to be made into pellets; the pelletization process involved the addition of water (temperature not stated) to facilitate making the pellets and a subsequent drying step (~100EC for up to 2 h) to reduce the water content. The pelletized diets were shipped back to Dow (Midland, MI) and stored inside closed (the containers were only opened to remove samples for analysis), polyethylene-lined, light-excluding cardboard drums at ambient room temperature for up to 104 days; also, there was no use of a "nitrogen gas" pad to create a deoxygenated enviroment. The technique for analyzing test material involved overnight extraction with 5% acetic acid in methanol, chromatographic separation by HPLC (column type, etc., not stated), and detection by UV-absorption (wavelength not stated). Recoveries of test material from "spiked" samples was ≥ 95% by this method; these extraction efficiencies were applied to sample calculations (p. 21). Homogeneity analysis (10 samples each) of the powder diets containing 0.25% of test material indicated that both OPP and OPP-Na diets were homogeneous; the OPP diet was 100% ± 2% of its target level while the OPP-Na diet was only 90% ± 3% of its target level (pp. 36-37). After being made into pellets, these same diets were 92-93% of their target levels,

indicating possibly some slight loss in content due to the pelletization process. Likewise, slight losses in content were observed when the content of the other diets were compared before and after pelletization (pp. 38-41). However, sampling at approximately 1 month, 2 months and 3 months postpelletization indicated that there was no appreciable loss in content for any of the diets containing either test material. Therefore, these analytical studies constitute sufficient analytical data to support the chronic rat studies conducted at the Tokyo Metropolitan Research Laboratory of Public Health (e.g., record 065929). **Supplementary information.** (Rinkus, 3/21/91).

129-129 087132 "Analytical Stability of Ortho Phenyl Phenol (OPP) and Sodium Salt of Ortho Phenyl Phenol (OPP-Na) in Rodent Chow Used in Japanese Toxicity Studies," (The Dow Chemical Company; file number HET T2.02-195-000-002; 3/22/90). This record is the protocol for record 091951. **Supplementary information. No worksheet.** (Rinkus, 3/21/91).

129-012 068363 "Quantitative Analysis of Sodium o-Phenylphenol Added to the Standard Animal Foods and Effect of Preservation," (Nawai et al., Ann. Rep. Tokyo Metr. Lab. P.H., **29**-2: 97-98, 1978). This record consists of two parts: a study in Japanese, with only the abstract, figures and tables written in English; and an English translation of the former in its entirety. This testing was conducted apparently to provide analytical data in support of ongoing testing in mice for the induction of dominant lethals (however, no feed studies for dominant lethal testing are on file with CDFA). Sodium OPP (Tokyo Kasei Kogyo K.K., Lot AL01, 97.1% purity) was mixed homogeneously into mouse food powder (Nippon Kurea's CE-2) at final target levels of 0.125%, 0.25%, 0.5%, 1%, 2%, and 4%. Mixtures were made into pellets by a process involving: applying steam heat (100EC) on the mixture; compressing the mixture into pellets; and drying the pellets at 100EC for 40-60 min. Prepared pellets were stored in a "food box," but the storage temperature was not specified. In general, it is not clear what were the preservation conditions highlighted in the title of this report. At 0, 10, 20, 30, and 55 days presumably after preparation (a footnote in a table discusses time in terms of days after the start of the dominant lethal testing), pellets were sampled randomly and stored under a nitrogen atmosphere until they could be analyzed. Analysis involved an extraction process using steam distillation and ident-ification by gas chromatography (flame ionization detection). Analytical testing indicated the following: 1) recovery of OPP standard (dissolved in NaOH solution; therefore, this was an OPP-Na standard) from spiked food was ≥ 96%; 2) there was no degradation of OPP-Na over the 55 days for any of the six test diets; and 3) the percent of target levels achieved decreased with decreasing concentration. Regarding item 3, for diets targeted to contain ≤ 0.5% concentrations of OPP-Na, only 72-76% of the targeted levels were achieved. The authors suggested that loss was occurring as a result of heat treatments during pellet preparation. **Supplemental information.** (Kishiyama, 1/10/89; Rinkus, 7/14/89).

129-012 068361 "Quality and Determination of o-Phenylphenol-Na in Animal Feeds," (Mizoiri et al., Ann. Rep. Tokyo Metr. Lab. P.H., **32**-2: 28-32, 1981). This record consists of two parts: a study in Japanese, with only the abstract, figures and tables written in English; and an English translation of the former in its entirety. Analytical testing consisted of two purposes: 1) to characterize the test material; and 2) to determine the recovery of OPP and OPP-Na from separate test diets supplied by the "Toxicity Department" of their organization. Regarding the former, only OPP-Na (Dow Chemical Co.; the lot was not specified, but presumably this was the lot used in the ongoing rodent bioassays that were mentioned in the report) was analyzed, in accordance with the "4th Food Additive Official Form," the meaning of which was not explained. The various data from this analysis were described inadequately, but the text stated that the observed values agreed with what was expected. The one noted exception was the melting point: 49-51EC was observed, when 55-58EC was expected. Although not explained, these melting point values appear to refer to the precipitate that results when an aqueous solution of OPP-Na is acidified: OPP-Na + HCl ! OPP (insol.) + NaCl; in which case, the expected value, 55-58EC, is the melting point of pure OPP. Some investigation of the impurities was done, but the methods were not described adequately. Apparently, an aqueous solution of the test material was acidified (therefore, OPP precipitated) and then was extracted wth n-hexane (OPP, but not OPP-Na, is soluble in this solvent; therefore, if the precipitate was not removed, the solvent would solubilize some OPP). The hexane fraction was washed with alkaline water, then plain water, and was concentrated for analysis by gas chromatography-mass spectrometry. Identified "neutral" impurities were: acetophenone, a and b-methyl naphthalenes, biphenyl, OPP, dibenzyl, dibenzofuran, diphenyl ether, phthalic acid n-butyl ester, phenyl [biphenyl-2] ether, and xanthone; why nonphenolic compounds would be contaminants was not discussed but it would seem inconsistent with the probable pathways for synthesizing OPP-Na. The authors concluded that the purity of the test material was 95.5%, with pure test material being the tetrahydrate of OPP-Na. However, the analysis did not

account for the alleged 4.5% impurity. Excess NaOH was said to be only 0.72% and the aforementioned neutral impurities amounted to only 0.03% (actually, the latter is an overestimate since it counted OPP as a major contaminant, which should not be possible if NaOH was also a contaminant). Consequently, the only useful information provided about the test material was that it was not analytical grade OPP-Na, and therefore it can be considered as some type of technical grade material. Regarding the ability to recover OPP and OPP-Na from feed, content analysis using three separate methods (steam distillation method used in record 68363; a dialysis method with 0.01 M NaOH; and extraction with methanol and detection with HPLC) indicated that >90% of the nominal concentrations were detected. However, since it was not stated how the feeds were prepared and stored and how much time had elapsed since their formulation, these results do not provide any information on the stability of the test materials in feed. One notable observation from the dialysis measurements was that with either OPP or OPP-Na, about 35% of the test material exists in the feed as OPP, which is insoluble in water, but is soluble in methanol or hexane. **Supplemental information.** (Kishiyama, 1/10/89; Rinkus, 7/17/89).

129-012 068362 "Uniformity of Test Article Concentrations in Pellet Diet used [in] Feeding Study," (Kamiya, N. and Hiraga, K., Ann. Rep. Tokyo Metr. Lab. P.H., **33**: 561-563, 1982). This record consists of two parts: a study in Japanese, with only the abstract, figures and tables written in English; and an English translation of the former in its entirety. OPP (ultrapure grade; Tokyo Kasei Kogyo), OPP-Na (purity and source not specified), and thiabendazole (purity not specified; Merck, Sharp & Dhome International) were added to rodent-feed powder (Nippon Kurea) at nominal concentrations of 1.25%, 1%, and 0.2%, respectively; and pellets were made according to the method described in record 68363. For each test material, 18 samples were taken from a rectangular container, representing 6 samples at three different depths. OPP and OPP-Na were extracted from crushed pellets into methanol and then quantitated by high-pressure liquid chromatography using the method described in record 68361. The results indicated that both OPP and OPP-Na were distributed homogeneously through the test diet. However, without data, the authors cautioned that it was difficult to make homogeneous test diets when the target levels were <1%. **Supplemental information.** (Kishiyama, 1/10/89; Rinkus, 7/17/89).

SUBCHRONIC STUDIES, IN SUPPORT OF CHRONIC STUDIES

129-012 068364 "Subacute Toxicity of Sodium o-Phenylphenate by Food Administration to Rats," (Iguchi et al., Ann. Rep. Tokyo Metr. Lab. P.H., **30**-2: 67-79, 1979). This record consists of two parts: a study in Japanese, with only the abstract, figures and tables in English; and an English translation of the former in its entirety. OPP-Na was presented in the diet for 13 weeks at the nominal concentrations of 0%, 0.125%, 0.25%, 0.5%, 1%, 2%, and 4%, to 10 F-344/Ducrj rats/sex/treatment level. Bodyweights as a percent of the control values showed a slight sex-related difference with the 2% diet: males' relative weight was 100%, while females' relative weight was 83%; with the 4% diet, both sexes had relative weights of ~83%. Absolute organ weights for the liver and the kidneys were increased statistically only in males on the 2% and 4% diets; urinary bladder weights were not measured. While serum GPT was decreased clearly in males on the diets containing $\geq$ 0.5% and in females on the diets containing $\geq$ 2% and serum GOT also was decreased in males on the diets containing $\geq$ 1%, the toxicological significance of decreases in these serum enzymes is not obvious. The pH of urine collected before sacrifice tended to be alkaline (pH 8) with increasing dietary concentration, but no occult blood in the urine was noted. The only hematological finding was a tendency towards anemia in females on the diets containing

≥ 0.5%. Based on this subchronic study, the maximum doses for the chronic feeding studies with OPP-Na that were done later (e.g., record 065929) were set to 2% and 1% for males and females, respectively. **NOEL = 1% diet (increased absolute kidney weight). Supplemental information.** (Kishiyama, 1/12/89; Rinkus, 7/19/89).

129-012 068374 "Subacute Toxicity of o-Phenylphenol by Food Administration to Male Rats," (Nakamura et al., Ann. Rep. Tokyo Metr. Lab. P.H., **32**-2: 33-39, 1981). This record consists of two parts: a study in Japanese, with only the abstract, figures and tables in English; and an English translation of the former in its entirety. OPP was presented in the diet for 13 weeks at the nominal concentrations of 0%, 0.625%, 1.25%, and 2.5%, to 10 male F-344/Ducrj rats/group. Mean bodyweights at the end of the study were 88% and 78% of the control value for the 1.25% and 2.5% groups, respectively. Absolute brain weight was decreased in the 2.5% group and absolute urinary-bladder postfixation weight was increased in the 1.25% and 2.5% groups; the weights of the liver and the kidneys relative to the bodyweight were increased in all groups receiving OPP. RBC count and hemoglobin concentration were decreased only in the 2.5% group. Increasing dietary intake of OPP tended to decrease both the pH of the urine (to pH 6) and the urinary concentration of protein; occult blood was detected in one rat in the 1.25% group and in another rat in the 2.5% group. No histological data was provided. **NOEL = <0.625% (increased relative kidney weight). Supplemental information.** (Kishiyama, 1/11/89; Rinkus, 7/20/89).

129-012 068373 "Subchronic Toxicity of o-Phenylphenol (OPP) by Food Administration to Rats," (Iguchi et al., Ann. Rep. Tokyo Metr. Lab. P.H., **35**: 407-415, 1984). This record consists of two parts: a study in Japanese, with only the abstract, figures and tables written in English; and an English translation of the former in its entirety. OPP was presented in the diet for 13 weeks at the nominal concentrations of 0%, 0.156%, 0.313%, 0.625%, 1.25%, and 2.5%, to 10 F-344/Ducrj rats/sex/treatment level. At the end of the study, the bodyweights of the high-dose males and females as a percent of the control values were 78% and 89%, respectively; no other groups showed any bodyweight effects. In males, the absolute and (or) relative organ weights of the kidneys, urinary bladder (postfixation), and liver increased with increasing intake of OPP, starting with the 0.313% diet for the liver effects; in females on the 2.5% diet, an increase was seen for the liver. In males on the 2.5% diet, brain weights were decreased, while in females on the 2.5% diet, heart, spleen, and possibly uterus weights were decreased; decreased spleen weight also was seen in females on the 1.25% diet as well. The pH of urine tended to be acidic (pH=6) only in the highest dose groups (both sexes); occult blood was detected in the urine of a few males on the 1.25% and 2.5% diets. The only hematological finding was a tendency towards anemia in both sexes on the 2.5% diet, and possibly the 1.25% diet. **NOEL = 0.313% (increased relative kidney weight). Supplemental information.** (Kishiyama, 1/11/89; Rinkus, 7/24/89).

129-012 068365 "Urinalysis of Male F344/DuCrj Rats Fed with Sodium o-Phenylphenate (OPP-Na)," (Tayama et al., Ann. Rep. Tokyo Metr. Lab. P.H., **35**: 425-430, 1984). This record consists of two parts: a study in Japanese, with only the abstract, photograph legends, and tables in English; and an English translation of the former in its entirety. The methods and the results are not described adequately, and the conclusions of the authors sometimes are not supported by the data. OPP-Na (Dow Chemical Co.; Dowicide A; lot no. MM01044) was presented in the diet for 52 weeks at the nominal concentrations of 0% and 2% to 6 and 30 male F-344/DuCrj rats, respectively. Urine was collected forcibly at the following times: weekly for the first 11 weeks, and then in weeks 13, 15, 17, 24, 30, 35, and 52. Urinalysis consisted of the following determinations: color, precipitate, pH, protein, glucose, ketones, and occult blood; however, the number of rats on the 2% diet whose urine actually was analyzed typically was <20. Also, naturally excreted urine

that collected below the individually caged rats was checked for pH weekly for the first 26 weeks using a pH meter, and then weekly afterwards using only pH test paper. The authors state that the forcibly excreted urine from the OPP-Na-treated rats always exhibited a higher pH (using a pH meter), in comparison to the urines of the untreated rats. However, based on the data (mean values) presented, this was only obvious in week 1 and may have been suggested by the data for weeks 2-4; in weeks 5-7, the difference in urinary pH between the two groups appears insignificant, possibly because by this time the pH of the control group's urine itself had become more alkaline. Positive findings of $\geq$ 1 forcibly excreted urine with occult blood were made with the OPP-Na-treated rats in weeks 6, 7, 10, 11, 13, 15, 17, 24, 30, 35, and 52; however, individual rats testing positive for occult blood changed with each round of testing. These results contrast with the testing for occult blood in the naturally excreted urine, wherein positive findings were observed with the OPP-Na-treated rats starting week 6 and continuing with each testing till the end of the study. Starting week 44, obviously bloody urines were observed; and the incidence of this hematuria increased in the following weeks. The authors implied that categorically rats exhibiting hematuria had bladder tumors when autopsied; however, the number of rats involved was not stated. Stones were detected macroscopically in weeks 11, 24, 30, 35, and 52. Fluorescence X-ray analysis indicated that the stones contained: Ca, P, Na, Mg, S, Fe, and Al. However, the color of the stones was not stated; therefore, it is not clear if these were the same "dark or greenish brown" stones that have been described in the carcinogenicity bioassays (e.g., record 065929). In general, CDFA can only conclude from this study that rats eating the 2% OPP-Na diet exhibited hematuria (both occult and frank) starting week 6 and many weeks later passed urinary stones that could be seen macroscopically. However, since no correlations among individual treated rats exhibiting acidic urine, occult or frank hematuria, and urinary stones were made, this study has provided little towards understanding the relationship of these findings to OPP-Na-induced carcinogenesis in the urinary tract of rats. **Supplemental information.** (Kishiyama, 1/12/89; Rinkus, 7/25/89).

CHRONIC DOG

129-010 004165 "Toxicological Studies of Orthophenylphenol (Dowicide 1)," (Dow, 2/52, published in J. Pharmacol. Experimental Therapeutics 104: 202 (1952), Hodge, H. C. et al.) OPP (>98%) fed in the diet at 0.02, 0.2 and 0.5 g/kg/day for one year; 2 mongrel dogs at each dose; no adverse effects reported including kidneys; UNACCEPTABLE, not upgradeable. Insufficient information for evaluation. (Remsen (Gee), 4/2/85).

129-012 068360 Protocol. "Ortho-Phenylphenol: Palatability and Two-Week Dietary Toxicity Study in Beagle Dogs." No worksheet.

129-012 068703 Addendum to protocol (129-012 068360). No worksheet.

129-063 069841. Protocol. Ortho-Phenylphenol: One-Year Oral Toxicity Study in Beagle Dogs." No worksheet.

**129-141 095220 "Ortho-Phenylphenol: Palatability/Probe, Four-Week and One-Year Oral Toxicity Studies in Beagle Dogs," (Cosse et al.; The Toxicology Research Laboratory/Dow; Report ID K-001024-039; 9/24/90). OPP, 100% purity, was administered by gavage at doses of 0 (peanut oil), 30, 100 and 300 mg/kg/d to 4 beagle dogs/sex/group for 12 months (5 d/w). Dose levels were based on preliminary studies which were included in the report. Two high-dose males died from

gavaging errors on test days 137-138. The only effects observed in the full study were the following: vomiting (both sexes), with the frequency and volume being greatest in the high-dose groups; and a decrease in serum phosphate levels for the mid- and high-dose female groups tested at 12 months. The toxicological significance of the decreased serum phosphate levels is not obvious since no other toxicological effects were noted, including none that would be indicative of an effect on the urinary tract. **NOAEL ≥ 300 mg/kg/d**. This study is considered **ACCEPTABLE**. (Rinkus, 1/24/91).

ONCOGENICITY, MOUSE

Note: In record 065930, which was not an acceptable study, there was evidence of a possible carcinogenic effect by OPP-Na at two sites: liver (males: hemangioma/hemangiosarcoma, plus possibly hepatocellular carcinoma) and stomach (females: squamous-cell papilloma) (discussed in worksheet W065930.832). In a second study, record 137329, which is an acceptable study, OPP was hepatocarcinogenic and there is a question about the possible induction of vascular tumors (all sites); but a carcinogenic effect in the stomach was not noted (discussed in worksheet W137329.832). (Rinkus, 4/24/96).

****129-221 137329** "Ortho-Phenylphenol: Two-Year Dietary Chronic Toxicity/Oncogenicity Study in B6C3F1 Mice" (Quast, J.F. and McGuirk, R.J.; The Toxicology Research Laboratory, The Dow Chemical Co.; laboratory project study ID number K-001024-047; 2/1/95). o-Phenylphenol (OPP), ≥ 99.7% purity, was administered in the diet for two years to achieve dose levels of 0, 250, 500 and 1000 mg/kg for ~50 B6C3F1 mice/sex/dose level. Dose levels were chosen based on the results observed in the mouse oncogenicity study of sodium OPP (record 065930). Survival ranged from 74% to 84% in the males and 56% to 72% in the females, was not statistically different among treatment groups and did not follow a dose-related pattern. Bodyweights were comparable among treatment groups at 13 weeks; subsequently, significant bodyweight reductions were noted in the high- and mid-dose groups (both sexes). At the end of the study, the mean bodyweights of the high-dose males, high-dose females, mid-dose males and mid-dose females were 87%, 80%, 93% and 87% of the corresponding control value, respectively. Serum alkaline phosphatase was statistically increased in each of the male groups and in the high-dose female group when assayed at one year, but not at two years. The specific gravity of urine was decreased significantly for the high- and mid-dose females when tested at two years. Significant, dose-related decreases in absolute kidney weight were seen with the high- and mid-dose male groups when measured at one and two years; when expressed as kidney weight relative to bodyweight, no statistical differences were noted. Absolute and/or relative kidney weight were increased in each of the female groups, with the increases in relative kidney weight achieving statistical significance at one year (low-, mid- and high-dose groups) and at two years (mid- and high-dose groups). Significantly increased absolute and/or relative liver weight was seen at each dose level at one year (both sexes) and at two years (females). Statistically significant nonneoplastic findings at two years included: decreased microvacuolation in kidney tubular cells for each of the OPP-exposed male groups; decreased severity of degeneration/regeneration of kidney tubules for each of the OPP-exposed groups (both sexes); accentuated lobular pattern consistent with liver hypertrophy/enzyme induction in each of the OPP-exposed groups (both sexes); decreased fatty change in the liver for the high- and mid-dose male groups; decreased incidence in the liver of foci of necrosis in the high- and mid-dose female groups; decreased incidence in the liver of vacuolated

or clear foci of cellular alteration in the high-dose male group; increased incidence of eosinophilic foci of cellular alteration in the high- and mid-dose male groups; and decreased pancreatic islet-cell hyperplasia in the high-dose male group. Neoplastic findings at two years included: dose-related increases in the incidence of liver adenomas in both sexes, with the incidences seen in the high- and mid-dose male groups achieving statistical significance; a 16% (8/49) incidence of liver carcinoma in the low-dose female group vs. 4% (2/48) in the female controls; a 4-12% incidence of hepatoblastoma in the OPP-exposed male groups; a 22% incidence of hemangioma/hemangiosarcoma (any site) in the low-dose male group, based on a partial examination of the spleens for the low- and mid-dose groups (both sexes); and a 18% and at least 14% incidence (latter based on the examination of organs from only 16 mice) of Harderian gland tumors in the control and low-dose male groups, respectively. **NOAEL < 250 mg/kg-d (hepatoblastoma).** How feed restriction/bodyweight reduction may have affected the interpretation of the results is discussed in worksheet W137329.832. This study is considered **ACCEPTABLE**. However, if the NOAEL is changed, the matter of the true incidences of hemangioma/hemangiosarcoma in the low- and mid-dose groups (both sexes) will need to be resolved. (Rinkus, 10/3/95).

129-200 130207 This record consists only of a table, entitled "Ortho-Phenylphenol (OPP): Two-Year Dietary Chronic Toxicity/Oncogenicity Study in B6C3F1 Mice--Preliminary, Unaudited Results from Male Mice." This record was accompanied by a letter from Paul A. Wright (Dow) to California Department of Pesticide Regulation, dated May 3, 1994. The letter acknowledges that the preliminary results indicate a tumorigenic response in the liver at all doses. **Supplemental information. No worksheet.** (Rinkus, 4/24/96).

129-032 035994 "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note," (Bionetics and NCI, published in: J. Nat. Cancer Inst. 42: 1101-1114, 4/30/69, Innes, J. R. M. et al). Two hybrid strains of mice were given 100 mg/Kg of OPP days 7 - 28 of age by gavage followed by 280 ppm in the diet after day 28 for 18 months; OPP was one of 120 other chemicals tested; at the level tested OPP gave no reported significant indication of oncogenicity. **UNACCEPTABLE**, no data. (Gee, 5/30/86).

129-032 035995 "The Tumor-Promoting Action of Phenol and Related Compounds for Mouse Skin," (R.K. Boutwell & D.K. Bosch, Cancer Res. 19:413-424, 1959). **Supplementary information. No worksheet.** (Rinkus, 4/1/91).

50438-007 003880/003883 Summaries of 004164 (chronic rat) and 035994.

129-037 045322 "NTP Technical Report on the Toxicology and Carcinogenesis Studies of ortho-phenylphenol alone and with 7,12-dimethylben(a)anthracene in Swiss CD-1 Mice," (Natl. Tox. Program, 3/86, NTP 84-099, NIH Publication No.85-2557). OPP (>99%, lot MM 09157); 50/sex/group; Swiss CD-1 mice were given dermal applications of 0.1 ml acetone, 55.5 mg/0.1 ml OPP in acetone, DMBA followed by acetone, OPP or TPA, 3 times per week for 102 weeks at the same site as DMBA for promotion; onco NOEL > 55.5 mg/day; no evidence of oncogenicity or promotion due to dermal application of OPP; OPP did cause an increase in non-neoplastic skin lesions over acetone control; **UNACCEPTABLE** (route of exposure with known poor absorption through skin, no indication of time of exposure and whether washed off is not clear). The single concentration used was the maximum soluble in acetone. This is not an oncogenicity study of the usual type and was designed for a different purpose, notably to test whether OPP acts as a promoter following initiation with a known carcinogen, DMBA. The DMBA/TPA combination gave the anticipated results of increased neoplasms and decreased survival. The OPP was irritating to the skin and

increased the incidence of skin lesions over the acetone control whether alone or following DMBA. Introductory discussion states that OPP is poorly absorbed though the skin. NCI recommended the study of whether it is a promoter for skin exposure. Study is complete but supplementary only for oncogenicity due to route of administration.
NOTE: From data in Record 036007, OPP-Na might have given a different result. (Gee, 6/2/86).

129-032 036010. Board Draft, 2/85, of 037 045332.

129-058 065930 "Long-Term Toxicity and Carcinogenicity Study of Sodium o-Phenylphenate in B6C3F1 Mice," (Nobuyuki Ito [author], First Department of Pathology, Nagoya City University Medical School, Nagoya, Japan, 1983). Sodium o-phenylphenol (OPP-Na), a stated purity of 97%, was given in the feed at the nominal concentrations of 0, 0.5, 1, and 2% to 50 B6C3F1 mice/sex/treatment group, for 96 weeks, followed by 8 weeks of basal diet until terminal sacrifice. Analytical testing was inadequately described but would indicate that the corresponding OPP-Na intake was 0, ~0.5, ~1.2, and ~2.4 grams/kg/day for both sexes. Percent survival at test week 96 was $\geq$ 80% for all treatment groups of both sexes, except the high-dose males, whose percent survival was 74%. Each of the three female groups eating OPP-Na had mean bodyweights at test week 90 that were depressed by 9-23% relative to the value for the controls; for males at test week 90, only the high-dose group showed any bodyweight depression (9%). The incidence of brain calcification was increased in the high-dose males and the mid- and high-dose females; only the 45% incidence in the high-dose females was statistically significant ($p<0.05$). For each of the three female groups eating OPP-Na, the heart, liver, and kidneys showed increased absolute weights and/or organ weights relative to bodyweight and serum alkaline phosphatase levels were increased; comparable effects in the males were not seen. A decrease in the specific gravity of urine was seen in each of the female groups eating OPP-Na and in the mid- and high-dose males. The incidences of hemangiomas/hemangiosarcomas in the livers of males and of squamous-cell papillomas in the stomachs of females were increased in each of the respective groups eating OPP-Na. **NOEL < 0.5% nominal (equivalent to N0.5 g/kg/day intake).** This record was considered originally (Rinkus, 8/9/89) to be unacceptable but upgradable upon submission of: 1) the OPP-Na stability data requested in record 065929; 2) method, chronology & storage conditions for formulating test diets; 3) explanation of histological data inconsistencies; and 4) complete historical control data from the conducting laboratory for observed tumor types. The requested data in item 1 now has been provided in record 091951, but the study is still considered **UNACCEPTABLE** pending submission of the other requested information. (Rinkus, 4/5/91).

50438-005 038132 "Long-term Toxicity and Carcinogenicity Study of Sodium o-Phenylphenol in B6C3F1 Mice," (Hagiwara et al., Fd. Chem. Toxic. 22: 809-814, 1984). Published version of 129-058 065930; it lacks data given as appendices in 065930. (Rinkus, 8/15/89).

129-032 036008 "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans," (IARC Working Group, 3/83, WHO, volume 30). Document states that inadequate data to evaluate carcinogenicity study reported by Innes et al. (record 035994).

REPRODUCTION, RAT

****129-232 141559** "A Two-Generation Dietary Reproduction Study in Sprague Dawley Rats Using

Technical Grade Ortho-Phenylphenol" (Eigenberg, D. A. And Lake, S.G.; Bayer Corporation, Agriculture Division, Toxicology, Study no. 93-672-VX, Sept. 28, 1995). This is the replacement study for record 072405/095639. o-Phenylphenol (OPP), purity ≥ 99.5%, was mixed into the feed such that ~30 CD Sprague-Dawley rats/sex/generation received nominal doses of 0, 20, 100 and 500 mg/kg/day. F0 rats were exposed for 10 weeks and ~21 weeks before the 1st and 2nd mating periods, respectively and were exposed for a total of 25-30 weeks (depending on the sex) before sacrifice. The postweaning exposure of the F1 rats before the 1st and 2nd mating periods lasted 12 weeks and ~22 weeks, respectively; and the F1 rats were 34-37 weeks old when sacrificed (depending on the sex). The only treatment-related, clinical-observation finding in the adults was an increased incidence of urine staining in the 500 mg/kg male groups (F0 and F1). Urine staining tended to start at study week 18 and to last till termination; in some cases, urine staining was also a finding at necropsy. Reduced bodyweight was noted in the F0 and F1 adults (both sexes) at the 500 mg/kg dose level. In the F0 females, the reduction was evident after three weeks of treatment; at 10 weeks and at termination, the mean bodyweight was 92-93% of the respective control values. The F0 males appeared to respond slower than the females; at 10 weeks and at termination, the mean bodyweight was 95% of the respective control values. F1 male and female 500 mg/kg groups exhibited reduced bodyweight as weanlings and began and ended the F1 premating period with bodyweights that were 89-91% of the respective control values. Gestation bodyweight gain was not affected by treatment but the lactation bodyweight gain of the F2b 500 mg/kg group may have been increased. Food consumption (amount consumed relative to bodyweight) tended to be increased in the F0 and F1 500 mg/kg groups, with the effect in males being greater than in females. Since an increase in food consumption occurred in the F0 males before the onset of bodyweight reduction, some of the increase in relative food consumption may not be attributable simply to the bodyweight reduction. Mating, fertility and gestation indices were not decreased by treatments. Fecundity (# live deliveries / # cohoused) was lower than expected in the F1 controls and increased with dose in the F2a and F2b periods. Estrous cycling, which was monitored for the last three weeks of the F0 and F1 premating periods, was not affected. The absolute and relative weights of the kidneys, testes and ovaries were not affected by treatment in either generation. The incidences of two necropsy findings were increased in the F1 500 mg/kg male group: urine-stained ventrums and urinary-bladder calculus (color not stated). The following nonneoplastic lesions were observed in the urinary bladder of the F0 and F1 500 mg/kg males: simple hyperplasia, nodular/papillary hyperplasia and chronic inflammation. Incipient effects also may have been produced in the kidneys and ureters of the 500 mg/kg males. No urinary tract cancers were noted. Lymphoma (a rare cancer for young Sprague-Dawley rats) occurred in two F1 500 mg/kg males. The main progeny effect was reduced pup bodyweight in each of the four periods at the 500 mg/kg dose level on lactation day 21, with marginal effects being present on lactation day 14. There was no effect on the following: live litter size, the incidence of stillbirths, perinatal death or the incidence of renal pelvic dilatation in the pups. When first reviewed (May 6, 1997), this study was considered unacceptable and upgrading required the submission of the supplemental information discussed in worksheet W141559.834. In response, the Registrant submitted record 165412. Based on the supplemental information, the following conclusions have been reached (discussed in worksheet W141559.S01). The selection of F1b weanlings to become F1 adults involved two groups: 30/sex/dose group, plus 2/sex/dose group; the latter served as some sort of replacement group until sacrificed (apparently) at about three weeks after the start of the F1 premating phase. In the first review, it was presumed that nude-rat syndrome (a rare trait) occurred in the 20 mg/kg group, involving 7 pups from two F0 dams. Nude-rat syndrome also had been seen in the first study (record 072405/095639) in the 490 mg/kg group, involving 10 pups from three F1 dams. However, upon reinspection of the data, it is questionable that the hypotrichosis occurring in record 141559 qualifies as nude-rat syndrome. The incidence of lactation-day-21 weanlings with stunted growth (≤ 40.0 grams) was increased in the 500 mg/kg groups. Although

two reproductive-toxicity studies, with two cases each of lymphoma (a rare cancer) associated with males and the same high dose, suggests of an incipient effect, the evidence is insufficient for concluding that OPP induced lymphoma in these reproductive-toxicity studies. **Parental NOEL = 100 mg/kg (nonneoplastic urinary-bladder lesions). Reproductive NOEL = ≥ 500 mg/kg (no effects at high dose). Progeny NOEL = 100 mg/kg (reduced pup bodyweight, including stunting)**. This study is marginally **ACCEPTABLE**. (Rinkus, 3/15/01).

129-278 165412 This record consists of an 8-page narrative section that provides a response to issues raised in worksheet W141559.834, with the following 10 appendices: Appendix I, a protocol amendment regarding F1b pups retained after weaning but not selected to be F1 adults; Appendix II, discussion and photographs of the hypotrichosis observed in the F0 low-dose group; Appendix III, individual pup bodyweights for lactation days 0, 4, 7, 14 and 21; Appendix IV, nude-rat syndrome bodyweights and necropsy findings; Appendix V, bodyweights and necrospy findings for pups as small as nude-rat-syndrome animals on lactation days 4 or 21; Appendix VI, the randomization scheme for assigning F1b weanlings to be F1 adults; Appendix VII, an amended page 92 from record 141559, indicating now that dam ID number 1120 was sacrificed in a moribund state; Appendix VIII, standard operating procedures for cohousing during mating triasl; Appendix IX, raw data for vaginal-smear inspections during cohousing for the four mating trials (TOX FORM 57's); and Appendix X, historical negative-control data regarding mononuclear cell leukemia for the conducting laboratory. **Supplemental information, discussed in worksheet w141559.s01.** (Rinkus, 3/16/01).

129-233 141560 "A Two-Generation Dietary Reproduction Study In Sprague-Dawley Rats Using Technical Grade ortho-Phenylphenol: Supplemental Information Requested by California EPA" (Eigenberg, D.A. & Lake, S.G.; Bayer Corp., Agricultural Division Toxicology, Stillwell, Kansas; study number: 93-672-VX; 9/28/95). This record contains the following: protocol amendments, protocol deviations and SOP deviations that apply to record 141559; and the estrous-cycle raw data for record 141559 and the procedure for analyzing these data. **Supplemental information. No worksheet.** (Rinkus, 5/20/97).

129-211 133253 This record contains unaudited data from the F1a, F1b and F2a periods of record 141559. These data were submitted at a meeting held on Nov- ember 18, 1994 between DPR MT staff (Drs. Gee, Iyer and Rinkus) and the Registrant's representatives (Dr. Sangha, Dr. Burin and Ms. Stevens). The meeting was held at the Registrant's request to discuss the low fertility that had occurred with the control and some OPP-treatment groups in the F2a mating trial in record 141559. These data were inspected originally in 1994 but they have not been given a formal review because these data are considered superseded by the data in the full study, record 141559. **Supplemental information. No worksheet.** (Rinkus, 5/20/97).

129-206 132174 "A Two-Generation Dietary Reproduction Study In Rats Using Technical Orthophenylphenol: Unaudited Interim Summary Tables" (Eigenberg, D.A.; Miles Inc., Agricultural Division Toxicology, Stillwell, Kansas; study number: 93-672-VX; report is undated [cover letter dated 9/13/94, from Christina L. Cocciardo to Fely Frank]). These data have not been reviewed because this submission was superseded by the submission of the full study, record 141559. (Rinkus, 5/20/97).

129-190 126178 "Protocol: A Two-Generation Reproduction Study in Rats Using Technical Orthophenylphenol" (Eigenberg, D.A.; Miles Inc., Agricultural Dvvision, Toxicology, Stillwell, Kansas; study number: 93-672-VX; report is unsigned and undated [it was stamped as received at DPR on

9/20/93]). This is the protocol for the replacement rat reproduction study (record 141559). DPR MT's review is contained in worksheet W126178.834. This worksheet served as the basis for discussions conducted by telephone on October 20, 1993 between DPR MT staff and the Registrant's scientists. **Supplemental information**. (Rinkus, 5/20/97).

129-198 127753 "Protocol: A Two-Generation Reproduction Study in Rats Using Technical Ortho-phenylphenol" (Eigenberg, D.A.; Miles Inc., Agricultural Division, Toxicology, Stillwell, Kansas; study number: 93-672-VX; no report date per se; signature page has 12/3/93 as latest date; accompanying letter by Christina L. Cocciardo (Miles) is dated 12/16/93. Letter indicates that this protocol is the same as record 126178 except that Dow Chemical is listed as a cosponsor. This was not reviewed. **Supplemental information. No worksheet.** (Rinkus, 5/20/97).

129-047 050575 Protocol for reproduction study at Mobay.

129-048 075867 This record concerns the study in records 072405/095639; its contents include the following: a protocol amendment regarding the shortening of the F1 premating before the F2a mating trial and the rest period before the F2b mating trial; and a progress report discussing the low fertility observed in the F1b mating trial. **Supplementary information. No worksheet.** (Rinkus, 4/1/91).

129-082 072405 "Two-Generation Dietary Reproduction Study in Rats Using Ortho-phenylphenol," (Mobay Corporation, Corporate Toxicology Department, Study no. 85-671-02, January 13, 1989). When this study was first submitted, it was considered unacceptable and to upgrade it would require the submission of data that addressed the many concerns that CDFA had with this study (Kishiyama, 2/23/89; Rinkus, 7/6/89). Subsequently, this study was resubmitted in its entirety, incorporating a variety of changes; this second submission is record 095639. See the summary to record 095639 for details. (Rinkus, 3/15/91).

129-139 095639 "Two-Generation Dietary Reproduction Study in Rats Using Ortho-phenyl-phenol--Revised Report" (Mobay Corporation, Corporate Toxicology Department, Study no. 85-671-02, January 13, 1989). This is the second submission of this reproduction study; the first was 129-082 072405. o-Phenylphenol, purity ≥ 99.4%, was mixed into the feed such that Sprague-Dawley rats of both sexes received (analytical) doses of 0, 35, 125 or 457 mg/kg/day. F0 rats were exposed for 15 and ~31 weeks before their 1st and 2nd matings, respectively, and were exposed for a total of 43 weeks before they were sacrificed (age: ~1 y); and F1 rats were exposed for 10 and ~22 weeks before their 1st and 2nd matings, respectively, and were exposed for a total of 31-37 weeks before they were sacrificed (age: 34-40 weeks). Premating bodyweights were decreased by treatments only in the high-dose groups: both sexes for F0 rats; and unequivocally the dams for F1 rats. Lactation BW change was increased for the F1b and F2b litters in the mid- and high dose groups. Mating and fertility indices were not affected by treatments for three of the mating trials; but the reduced fertility in the high-dose group for the F1b mating trial is difficult to interpret due to low fertility in the controls and the reduced estrus cycling observed for each of the treatment groups before the F1b mating trial. Organs whose absolute weights tended to increase with treatments were the testes, ovaries, kidneys (F0 and F1 males), and liver (F1 males). The incidence of ovarian cysts was increased in the F0 high-dose dams. Nonneoplastic lesions were observed in the urinary bladder and kidneys, including 4 cases of papil-lomatosis or papilloma formation in the urinary tract of F0 rats from the mid- and high-dose groups. **Parental NOAEL = 35 mg/kg (one dam exhibited papillomatosis in its urinary bladder after 14 weeks of eating a diet of ≤ 2000 ppm).** Based on the raw data, the incidence of "stillbirths" for the F2a and F2b

litters appeared to be increased in the mid- and high-dose groups; therefore, the reproductive NOAEL appeared to be 35 mg/kg. Day-14 and day-21 pup weights were reduced in the high-dose groups for each of the four periods. The incidence of kidney dilatation observed grossly in day-21 weanlings was increased in each of the OPP-treatment groups for both the F2a and F2b litters. **Progeny NOAEL = < 35 mg/kg.** When previously reviewed (3/15/91), this study was considered unacceptable and to upgrade the following had been requested for submission: an appropriate audit of the data; all protocol changes and deviations; and supplementary information, including raw data, in various areas, as detailed in worksheet W095639.834. These data have now been submitted (records 112073, 113297 & 113884) and are discussed in worksheet W095639.S01. Statistical analyses confirm the identification of weanling kidney dilatation as an endpoint for the progeny NOAEL. However, the following clarification regarding the endpoint for the reproductive NOAEL is indicated: what is increased in the F2a and F2b mid- and high-dose groups is perinatal deaths occurring on lactation days 0-4, not simply stillbirths. **Reproductive NOAEL = 35 mg/kg (perinatal deaths).** This study is considered **UNACCEPTABLE AND NOT UPGRADABLE.** (Rinkus, 7/7/92).

129-138 095645 This record contains supplementary information to record 072405. It consists of 6 parts: 1) responses by the Sponsor to the matters raised in the worksheet to record 072405; 2) data and statistical analyses for gestational and lactational bodyweights and litter parameters; 3) necropsy data regarding kidney dilatation in day 21-weanlings (as well as some day-4 culled pups & pups found dead); 4) pretesting serological data attesting to the well being of the rats before being shipped from the supplier; 5) a letter from the American Association for Accreditation of Laboratory Animal Care (AAALAC) indicating that the conducting laboratory is AAALAC accredited; and 6) a letter from the animal supplier (Charles River, Wilmington, MA) noting that hypotrichosis has a low incidence among their rats. **Supplementary information. No worksheet.** (Rinkus, 3/15/91).

129-138 095663 This record concerns the histological examination of 4 slides of the urinary tract, representing 4 rats from records 072405/095639; the examinations were done by Dr. Cohen (University of Nebraska Medical Center) and Drs. Kociba and Quast (The Dow Chemical Company). **Supplementary information. No worksheet.** (Rinkus, 3/15/91).

129-138 095664 "Cell Proliferation Induced by Uracil-Calculi and Subsequent Development of Reversible Papillomatosis in the Rat Urinary Bladder," (Shirai et al., Cancer Research, 49:378-383, 1989). This record along with record 095665 are supposed to constitute the "classification scheme" for the histopathological examinations given in record 095663. **Supplementary information. No worksheet.** (Rinkus, 3/15/91).

129-138 095665 "Uracil-Induced Urolithiasis and the Development of Reversible Papillomatosis in the Urinary Bladder of F344 Rats," (Shirai et al., Cancer Research, 46:2062-2067, 1986). This record along with record 095664 are supposed to constitute the "classification scheme" for the histopathological examinations given in record 095663. **Supplementary information. No worksheet.** (Rinkus, 3/15/91).

129-138 095666 "Toxic and Non-Toxic Changes Induced in the Urothelium by Xenobiotics," (Samuel M. Cohen, University of Nebraska Medical Center, Paper presented at the 1989 Society of Toxicology meeting). **Supplementary information. No worksheet.** (Rinkus, 3/15/91).

129-138 095667 This record concerns the occurrence of stones in the urinary tract of untreated

SD rats; it consists of two sections: 1) The Pathology of Laboratory Animals, Volume I, p. 159, Benirschke et al. (Eds.), Springer-Verlag, New York, year not stated; and 2) The Laboratory Rat, Volume I, pp. 389-390, Baker et al. (Eds.), Academic Press, New York, 1979. **Supplementary information. No worksheet.** (Rinkus, 3/15/91).

129-138 095668 This record concerns the occurrence of pinworms in laboratory rats; it consists of two sections: 1) Laboratory Animal Medicine, pp. 111-113, Fox et al. (Eds.), Academic Press, New York, year not stated; and 2) The Laboratory Rat, Volume I, pp. 321-322, Baker et al. (Eds.), Academic Press, Ney York, 1979. **Supplementary information. No worksheet.** (Rinkus, 3/15/91).

129-160 112073 This record contains the following: 1) individual responses to the matters raised in worksheet W095639.834; 2) the protocol to the study presented in records 095639 and 072405; 3) 17 protocol amendments and 7 protocol deviations; 4) raw data regarding lactation for the F1b period; 5) raw data regarding designation of mating status for the entire study; 6) raw data regarding external and gross pathology observations for dams 0069, 2252 and 3259; 7) raw data regarding litter necropsy observations for the litters of dams 0069, 2252, and 3259; 8) corrected tables for stillborn pups and statistical analyses of these corrected data; 9) raw data regarding kidney dilatation in 21-day old pups for the entire study; 10) an overview of kidney dilatation observed in the pups in the study as well as in the historical control data; 11) an evaluation by a consultant to the Registrants of the kidney dilatation observed in weanlings in the study; 12) a table listing corrections to the delivery data presented in record 095639; 13) a summary of stillborn pups in the study and a statistical analysis thereof; 14) 4 articles from the literature regarding the use of the litter as the experimental unit for statistical analyses of pup data; and 15) raw data regarding litter necropsy observations for all pups in the study which were older than 21 days when sacrificed. **Supplemental information. No worksheet.** (Rinkus, 7/7/92).

129-165 113297 This record contains a variety of corrections to the data presented in records 095639 and 112073. These corrections were identified by the Registrant in the course of auditing the pathology tables and appendices in record 095639. **Supplemental information. No worksheet.** (Rinkus, 7/7/92).

129-167 113884 This record contains the following: 1) written responses to questions posed by Dr. Rinkus (DPR MT) in a telephone conversation with the Registrant's toxicologists (3/11/92) regarding record 112073; 2) raw data regarding lactation for the F1b period for dams 0063 and 3062-3085; and 3) the standard operating procedure used for the mating trials in record 095639. **Supplemental information. No worksheet.** (Rinkus, 7/7/92).

ANALYTICAL STUDIES, IN SUPPORT OF THE REPRODUCTION STUDY

129-138 095669 "Analytical Chemistry Report: The Evaporation of Methyl Isobutyl Ketone (MIBK) from Rodent Ration Stored in Rat Feeders," (K.D. Moore; Mobay Chemical Corporation; Toxicology Report No. 710; 2/10/86). This record was submitted as evidence that it is highly unlikely that any acetone was present in the diets that the rats ate in the reproduction study (records 072405/095639) even though acetone was used to prepare the diets. **Supplemental information. No worksheet.** (Rinkus, 3/15/91).

129-138 076032 "The Stability of Ortho-phenylphenol in Rodent Ration--A Comparison of Three Methods of Analysis," (K.D. Moore; Mobay Corporation; Laboratory Project ID Report No. 100271; 8/29/90). This stability study was performed in response to concerns raised by CDFA in its review of the first submission of the rat reproduction study, record 072405, wherein the analytical data had indicated that o-phenylphenol (OPP) was not stable in rodent chow. While these analytical findings were not one of the reasons for not accepting record 072405, they were still important because they indicated that OPP-containing diets were not stable enough to be stored for 3-month periods, as had been done in some rat chronic studies conducted by Japanese researchers that the Sponsors had submitted to fill SB950 data requirements (e.g., record 065929). Since a loss of OPP content over time could be the result of the actual OPP degradation as well as an increasing inefficiency in recovering OPP from the diet, the latter possibility was tested by using three different methods to recover OPP from aging diets. A diet made up to contain 5031 ppm (40.241 g OPP mixed into 7880 g chow plus 79 g corn oil [presumably]) was analyzed for content over a 28- day period. The three extraction methods were: 1) methanol extraction (OPP is highly soluble in methanol); 2) 0.1 M NaOH extraction (OPP is ionized in alkaline water, which maximizes its water solubility); and 3) acetonitrile extraction (this was the method used in the analytical studies reported in record 072405). What exactly was done and whether recovery efficiencies were determined for each day that analyses were done were not clearly stated. For some "5000 ppm" diet, the recovery efficiencies were $\geq$ 94% for each of the methods (pp. 488, 493 & 498), but from the day-0 results of the aging study (p. 483), method 2 appeared to recover only 86% of the target value (4303/5031). At the end of 28 days, method 3 only recovered 70% of the original target value (3505/5031); the loss corresponds to what had been observed in record 072405. The proof that this was not OPP degradation was that the recovery of OPP was still 95% with method 1 (4792/5031). Method 2 showed a seeming increase in OPP content over time (4813 ppm on day 28), but this may be artefactual because the recovery efficiency on day 0 may have been abnormally low. Assuming that the 5031 ppm diet and a control diet (0 ppm diet) were prepared the way diets were prepared in record 072405 (i.e., with acetone and corn oil) and that there were no interfering peaks coeluting with OPP from control diets over time with method 1, these analytical findings would indicate that OPP in diets prepared in the manner described in record 072405 is stable for at least 28 days.
Supplementary information. (Rinkus, 3/15/91).

TERATOGENICITY, RABBIT

****129-148 097303** "Ortho-Phenylphenol (OPP): Gavage Teratology Study in New Zealand White Rabbits," (Zablotny et al.; The Toxicology Research Laboratory, Dow Chemical Company; Laboratory Project Study ID number K-001024-045; 4/23/91). In the first phase of testing, OPP was given by gavage on gestation days 7-19 to 16 inseminated NZW rabbits/group at 0 (corn oil), 25, 100 and 250 mg/kg and does were sacrificed on gestation day 28. In supplementary testing, OPP was administered only to 2 and 8 inseminated does/group at 0 and 250 mg/kg, respectively; data from this second phase of testing were combined with the data from the first phase. Treatment levels were chosen on the basis of a probe teratology study (record 097302). Does, especially those in the high-dose group, exhibited several effects (blood in the excrement pans, hairballs in the stomach, increased mortality, ulceration and hemorrhaging in the stomach, hemolyzed blood in the intestines); but it is unclear whether most of these were actually OPP-induced. One effect that did appear to be OPP-induced was renal tubular degeneration and inflammation. **Maternal NOAEL = 100 mg/kg (renal tubular degeneration/inflammation).** The only fetal effect noted in

the study was an increase in the frequency of litters with resorptions in the 100 and 250 mg/kg groups. **Fetal NOAEL = 25 mg/kg (increase in resorptions).** When first reviewed (7/16/91), this study was considered UNACCEPTABLE but UPGRADABLE upon submission of: 1) raw data regarding when some does died; and 2) statistical analyses and historical control data regarding resorptions. These data now have been submitted (records 112322 & 113826) and, as discussed in worksheet W097303.S01, the matters that they addressed now are considered resolved. This study now is considered **ACCEPTABLE**. (Rinkus, 8/4/92).

129-162 112322 This record contains the following: 1) individual responses to the matters raised in W097303.833; 2) Registrant's comments about whether rabbits had been randomly assigned to treatment groups and about whether doses of $\geq$ 250 mg/kg cause multiple toxicological responses in the does; 3) raw data for two high-dose does that died on gestation days 15-16; 4) a 1975 memorandum from Dr. Joseph K. Haseman regarding the uses of the Fisher's exact test in teratology studies; 5) historical control data for the conducting laboratory regarding the incidence of litters with resorptions; 6) statistical analyses of the data regarding resorptions in record 097303; and 7) four articles from the open literature regarding hairballs in rabbits. **Supplemental information. No worksheet.** (Rinkus, 8/4/92).

129-166 113826. This record contains two letters. The one dated 3/19/92 is from the study director for record 097303; the letter explains why the wrong identification number appears in the raw data for doe 90A6484 contained in record 112322 (p. 16). The other letter is discussed under this record number in the section "Combined Chronic-Oncogenicity, Rodents." **Supplemental information. No worksheet.** (Rinkus, 8/4/92).

129-132 095057 "Ortho-Phenylphenol (OPP): Gavage Teratology Study in New Zealand White Rabbits," (The Dow Chemical Company, file number HET K-001024-045; 8/13/90). This record is the protocol to record 097303. **Supplementary information. No worksheet.** (Rinkus, 3/25/91).

129-148 097302 "Ortho-Phenylphenol (OPP): Gavage Teratology Probe Study in New Zealand White Rabbits," (The Dow Chemical Company; laboratory project study ID: HET K-001024-044; 4/2/91). This study was used to set the dose levels in the full study in record 097303. Seven inseminated does/group were gavaged once daily at 0, 250, 500 and 750 mg/kg on gestation days 7-19 and were sacrificed on day 20. **Supplementary information. No worksheet.** (Rinkus, 7/16/91).

129-130 087182 "Ortho-Phenylphenol (OPP): Gavage Teratology Probe Study in New Zealand White Rabbits," (The Dow Chemical Company, file number HET K-001024-044; 6/29/90). This record is the protocol to record 097302. **Supplementary information. No worksheet.** (Rinkus, 3/25/91).

129-140 091950 This record contains two protocol addenda to the full teratology study in record 097303. The first addendum concerns the addition of 2 does to the 0 mg/kg/day group and 8 does to the 250 mg/kg/day group. Does were added to these groups because the number of litters with viable fetuses in these groups were only 12 and 10, respectively; FIFRA guidelines recommend $\geq$ 12 pregnant does per dose level. The second addendum concerns histopathological examinations of the kidneys of all rabbits in the study; this was done to establish a NOAEL for the kidney lesions observed in the teratology probe study. **Supplementary information. No worksheet.** (Rinkus, 3/25/91).

129-148 097301 "Ortho-Phenylphenol (OPP): 13-Day Range Finding Oral Gavage Study in New Zealand White Rabbits," (The Dow Chemical Company; laboratory project study ID: HET K-001024-043; 3/19/91). This study was used to set dose levels for the probe teratology study found in record 097302. Two nonpregnant female rabbits/group were gavaged at 0, 100, 500, and 1000 mg/kg for 13 consecutive days and were sacrificed on day 14. **Supplementary information. No worksheet.** (Rinkus, 7/16/91).

129-130 087181 "Ortho-Phenylphenol (OPP): 13-Day Range Finding Oral Gavage Study in New Zealand White Rabbits," (The Dow Chemical Company, file number HET K-001024-043; 5/21/90). This record is the protocol to record 097301. **Supplementary information. No worksheet.** (Rinkus, 3/25/91).

TERATOGENICITY, RODENT

RAT

129-032 036013 "Teratogenicity and Dominant-Lethal Studies with o-Phenylphenol," (Journal article (1978) published in J. Pesticide Sci. 3: 365-370, Kaneda, M. et al). OPP (99.7%); 20 female Wistar rats per group were dosed by gavage with 0, 150, 300, 600 or 1200 mg OPP/Kg on days 6 through 15 of gestation; all but 1 female at high dose died; body weights of dams in the 600 and 300 mg/Kg groups were significantly lower; fetal resorption was elevated and pup weights were reduced in the 600 mg/kg group; abnormalities did not differ among surviving pups; sys NOEL = 150 Mg/Kg (maternal toxicity). From limited information, dev. tox. NOEL appears to be 300 mg/kg. **UNACCEPTABLE** with no adverse teratogenic effect (no analysis of dosing solutions, no individual data). (Gee, 6/3/86).

129-031 028378. Duplicate of 036012 & 036013.

129-032 036020 "The Effects of Orally Administered Orthophenylphenol on Rat Embryonal and Fetal Development", (Tox Research Lab-Dow, 8/30/78, John, J. A. et al). OPP (>99%); 34 control and 25-27 pregnant Sprague-Dawley rats were given 0, 100, 300, or 700 mg/Kg by oral gavage days 6-15; no adverse effects reported for developmental tox; sys NOEL = 300 mg/Kg (maternal body weight), Dev. NOEL = 700 mg/kg; originally reviewed as unacceptable by Gee, 6/3/86, because of missing data on food consumption and dosing solution preparation. Now up-graded to **ACCEPTABLE (missing data on analysis of dosing material and individual values on food consumption contained in Record # 054898, 129-048). Although the maternal effects re-ported are marginal in terms of toxicity, 1200 mg/kg to rats was lethal to 10/11 pregnant animals -see 036013 above. (Gee, 6/3/86 and 3/30/87).

129-048 054898 Supplement to 036020. Individual food consumption and records for preparation of dosing solutions.

129-032 036021 Partial duplicate of 036020. Publication in Fundamental and Appl. Toxicol. 1: 282-285 (1981). (Gee, 6/3/86).

129-031 028379 Exact duplicate of 036021.

MOUSE

50438-005 038133, "Teratological Tests of Ortho-Phenylphenol and Its Sodium Salt in Mice", (Journal article (1978) published in Ann. Rept. Tokyo Metr. Res. Lab. P. H. 29: 89-96, Ogata, A. et al). OPP (Lot FB103) and its sodium salt (lot MM1044); 20/group given 0, 1450, 1740 or 2100 mg/Kg/day OPP in olive oil or 0, 100, 200 or 400 mg/Kg/day OPP-Na in water by oral gavage days 7-15; high mortality at high dose with both test articles - 16/21 with OPP and 16/21 with OPP-Na; some at mid-dose; fetal effects at all doses with cleft palate, open eye and exencephalia being identified - skeletal findings are attributed to maternal toxicity; **positive fetal findings occurred at the low doses where marginal maternal toxicity, especially with OPP-Na**. Systemic NOEL not clearly established due to lack of data. **Dev. NOEL <100 mg/kg. UNACCEPTABLE** (dev. NOEL not established, no individual data, tables hard to read with Japanese and English headings in small print, no historical controls, inadequate number of fetuses for visceral exam, no purity of test articles, dose selection poor), **not upgradeable.** (Gee, 5/30/86 and Parker, 6/13/86).

129-032 036022. Duplicate of 038133.

GENOTOXICITY, GENE MUTATION

Note: Results with gene mutation studies present mixed results in both bacterial and eukaryotic systems. Although no one study is adequate, collectively they contain sufficient data to determine that OPP is not mutagenic in bacteria but is genotoxic in mammalian cells in vitro. (Gee).

Microbial Systems

50438-005 038122 "Molecular Mechanisms involved in the Toxicity and Carcinogenicity of Ortho-phenylphenol and its Sodium Salt", (Journal article (1983) published in Chem.-Biol. Interactions 43:99-119, Reitz, R. H. et al). OPP-Na (lot MM09220B, 72%, 25.6% water and 1.05% NaOH); Strains TA98, 100, 1535, 1537 and 1538 of Salmonella typhimurium were tested at 0.25, 2.5, 25, 125 and 250 µg OPP-Na/plate with and without S9 with 30 minutes preincubation before plating; no increases in reversion rates were noted at these exposure levels; cytotoxicity at 125 and 250; triplicate plates. UNACCEPTABLE, no repeat trial. (Gee, 5/30/86).

129-032 035998. Duplicate of 038122 in 50438 - same data in report form.

129-032 036002. Exact duplicate of 038122.

129-047 050581. Duplicate of 038122.

129-032 036000. Exact duplicate of 038122.

129-032 036011, "Mutagenicity Evaluation of Ortho-Phenylphenol: Final Report", (Litton Bionetics, 3/31/76, LBI Project No. 2547.). OPP (no purity or lot number) tested in Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538 at 0, 0.025, 0.25, 2.5 or 25 µg/plate +/- rat S9; one trial, one plate; no increase in reversion rate reported; UNACCEPTABLE (missing information, no repeat test, no evidence that cytotoxic level achieved), not upgradeable. (Gee, 6/2/86).

129-032 045825 "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ortho-phenylphenol Alone and with 7,12-Dimethylbenz(a)anthracene in Swiss CD-1 Mice" (Appendix K, Genetic Toxicology of o-phenylphenol), (Natl.Toxicology Prog., 2/85, Board Draft, NTP 84-099 - see 129-037 for final version of report, dated March, 1986). Summary only: Strains TA 98, 100, 1535, and 1538 of Salmonella typhimurium were tested at 0, 3.3, 10, 33, 40, 60, 80, 100 120, 140 or 200 µg OPP/plate +/- S9 (rat and hamster) with 20 minute preincubation before plating; test article was weakly mutagenic at 80 µg/plate and higher in TA 1535 (minus S9). The assay was performed twice with triplicate plates but only the mean and SD of one experiment is presented in a table as an Appendix. UNACCEPTABLE because incomplete report. (JG, 6/2/86).

129-032 036010. Main report of 045825

129-032 036014, "Mutagenicity testing on o-phenylphenol", (summary only--abstract in Mutation Res. 54: 277 (1978), Shirasu, Y., et al). Salmonella host-mediated in mice. No effect reported. No data.

129-032 036018, "Mutagenicity testing on o-phenylphenol", (abstract from Mutation Res. 54: 277 (1978), Shirasu, Y. et al). E. coli WP2 hcr^- with and without S9. No data. No effect.

129-047 050580 "Detection of Chemical Mutagens--Use of Concentration Gradient Plates in a High Capacity Screen," (J.C. Cline & R.E. McMahon, Res. Comm. Chem. Path. Pharmacol. 16:523-533, 1977. **Supplementary information. No worksheet.** (Rinkus, 4/1/91).

Mammalian Systems

129-032 036019, "Orthophenylphenol Mutagenicity in a Human Cell Strain", (Journal article (1984): published in Mutation Res. 156:123-127, Suzuki, H. et al). The potential for OPP to induce ouabain-resistant mutants in ultraviolet-sensitive human RSa cells was examined; cells were exposed to 0, 15, 20, 25, or 30 µg OPP/ml with ethanol as solvent for 24 hrs; mutation frequencies increased in a dose-related fashion. No data--only graphs. MF appeared to be about 100x control at 30 µg with a linear increase with concentration. UNACCEPTABLE. (Gee, 6/3/86).

129-032 045826 "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ortho-phenylphenol Alone and with 7,12-Dimethylbenz(a)anthracene in Swiss CD-1 Mice" (Appendix K, Genetic Toxicology of o-phenylphenol), (Natl. Tox. Program, 2/85, Board Draft, NTP 84-099--see 129-037 for final version of report dated March, 1986, summary only). L5178Y/TK +/- mouse lymphoma cells were exposed to 0, 0.32, 0.63, 1.25, 2.50 and 5.00 µg/ml OPP with S9 and 0, 20, 30, 40, 50 or 60 µg/ml without S9; weakly mutagenic at levels of 40 µg/ml and above without activation and at 5 µg/ml with metabolic activation. A second trial -S9 was performed but no data presented. UNACCEPTABLE, incomplete. (Gee, 6/2/86).

129-032 036010. Main report of 045826.

129-032 045827 "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ortho-phenylphenol Alone and with 7,12-Dimethylbenz(a)anthracene in Swiss CD-1 Mice", (Natl. Tox. Program, 2/85, summary only). The sex-linked recessive lethal assay with Drosophila was utilized to test mutagenic potential of OPP; insects were either fed the test article at 250 ppm or received injections of 500 ppm; three broods of 3, 2, 2 days; at these levels the test article failed to increase the incidence of mutations. UNACCEPTABLE (missing data), No adverse effect. (Gee, 6/2/86).

129-032 036010. Main report of 045827.

GENOTOXICITY, CHROMOSOME

Note: This data requirement was considered satisfied previously, with a possible adverse effect indicated based on studies in mammalian cells (record 045828). Since then, at least two more studies have appeared in the open literature which also indicate that OPP itself or its metabolites are capable of causing chromosomal damage in mammalian cells treated in vitro: Tayama-Nawai et al., Mutation Res. 141:95-99, 1984; and Tayama et al., Mutation Res. 223:23-33, 1989. (Rinkus, 8/15/89).

129-032 045828 "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ortho-phenylphenol Alone and with 7,12-Dimethylbenz(a)anthracene in Swiss CD-1 Mice" , (Natl. Tox. Program, 2/85, summary only). The potential for OPP to induce sister-chromatid exchange (14.9, 20.0 and 29.9 µg/ml without S9 and 24.9, 49.8 and 75.4 µg/ml + rat liver S9) or chromosomal aberrations (60.0, 70.2 and 80.0 µg/ml without S9 and 70.2, 80.0 and 90.0 µg/ml +S9) in cultured Chinese hamster ovary (CHO) cells was examined; without S9, OPP tended to increase sister- chromatid exchange but not aberrations. SCE/cell for DMSO control was 8.9/cell and 11.4 at 29.9 µg/ml. UNACCEPTABLE (inadequate data and methods description), with weak effect on SCE formation. (Gee, 6/2/86).

129-032 036012 "Teratogenicity and Dominant-Lethal Studies with o-phenylphenol", (Journal article published in J. Pesticide Sci. 3:365-370 (1978), Kaneda, M. et al). Dominant lethal in groups of 15 male CH3 mice were administered 0, 100 or 500 mg OPP (>99%)/Kg by gavage for 5 successive days; immediately following the exposure period each male was caged with 2 females for 1 week; mating trials continued for 6 weeks; pregnant females were killed on day 12 or 13 of gestation to examine for dominant-lethal mutations; increased frequencies were not recorded in test groups. Body weight of males was depressed to 92% of controls after five days at the high dose. UNACCEPTABLE (no analysis of dosing solutions, no individual data), negative for adverse effect. (Gee, 6/3/86).

129-032 036016. Partial duplicate of 036012.

129-031 028378. Duplicate of 036012.

129-032 036015 "Mutagenicity Testing of o-phenylphenol", (Abstract in Mutation Res. 54: 277 (1978), Shirasu, Y. et al). Rat in vivo cytogenetics. A single dose at 0, 250, 500, 1000, 2000 or 4000 mg/kg or 5 doses at 0, 50, 100, 200, 400 or 800 mg/kg and sacrificed at 24 hours. No effect was found. UNACCEPTABLE, incomplete.

GENOTOXICITY, DNA/OTHER

Note: Based on the study by Reitz et al. (Chem.-Biol. Interactions 43: 99-119, 1983) the negative findings for Unscheduled DNA Synthesis and for DNA binding were used previously to close this data gap. These findings along with others were presented by the Sponsors in support of the hypothesis of a non-genotoxic mechanism for the formation of bladder tumors. However, CDFA has noted in its rebuttal of 8/30/89 that a genotoxicity mechanism that does not involve DNA binding also appears plausible. Morimoto et al. (Jpn. J. Cancer Res. 78: 1027-1030, 1987) have shown using the alkaline elution assay that intrabladder injection of the quinone of 2,5-dihydroxybiphenyl, a suspected metabolite of OPP, induced DNA single-strand breaks in the cells isolated from the epithelium of the bladder; also, epithelial hyperplasia was observed 5 days later in the bladder after a single treatment with this metabolite. These results may indicate that the treatment with the quinone led to the formation of radicals which attacked the DNA to cause the genotoxicity. Morimoto et al. have proposed that the "active oxygen species" were probably responsible for the bladder carcinogensis. Thus, CDFA does not agree necessarily with the position of the Sponsors that the mechanism of action for OPP does not involve genotoxicity. (Rinkus, 8/30/89).

50438-005 038123, "Molecular Mechanisms involved in the Toxicity of Orthophenylphenol and its Sodium Salt", (Journal article (1983) published in Chem.-Biol. Interactions 43: 99-119 (1983), Reitz, R. H. et al). Using cultures of rat hepatocytes, OPP-Na (lot MM0922OB, 72% SOPP, 25.6% water and 1.05% NaOH) was evaluated for its potential to induce UDS; 10^{-7}, 10^{-6}, 10^{-5} and 10^{-4} M, higher concentrations were cytotoxic; test article did not increase UDS. UNACCEPTABLE (missing data), No adverse effect. (Gee, 5/30/86).

129-032 035999 Duplicate of 038123.

129-032 036003 Duplicate of 038123.

129-032 036017 "Mutagenicity Testing on o-phenylphenol", (Abstract in Mutation Res. 54: 277 (1978), Shirasu, Y. et al). Rec assay in B. subtilis with and without activation; results stated to be negative --no data. (Gee, 6/3/86).

129-032 036001 [identical to 035999], "Molecular Mechanisms Involved in the Toxicity of Ortho-phenylphenol and its Sodium Salt--DNA alkylation," (Dow, 1981, published in: Chem.-Biol. Interactions 43:99-119 (1983) by Reitz, R. H. et al). [14C]-OPP (99.8%, lot MM09250) or [14C]-SOPP (lot MM09220OB, 72% SOPP, 25.6% water and 1.05% NaOH), 500 mg/kg, given by oral gavage to groups of 8 male rats per test compound; sacrificed after 16 hours and DNA extracted from the bladders--DNA pooled; no details of methods for DNA extraction or for counting the DNA; **two experiments with negative results** reported in both in terms of dpm; samples counted (method not described) for 100 minutes per sample--report states the accumulated counts were sufficient to detect 1-2 dpm at the 95% confidence limit; **unacceptable** as reported due to lack of methods. (Gee, 3/30/87).
EPA memo [copy in document 129-048] of March 22, 1982, indicates the test was evaluated as "acceptable" and "adequately" conducted "within the context of the reservations when using this testing approach...." Whether they reviewed the identical document is not known.

50438-005 038125 "Molecular Mechanisms Involved in the Toxicity of Orthophenylphenol and its Sodium Salt - Cellular Regeneration", (Dow, 1981, published in: Chem.-Biol. Interactions 43: 99-119 (1983), Reitz, R. H. et al). Orthophenylphenol (OPP) and sodium orthophenylphenol (SOPP) were given by oral gavage at 500 mg/kg to 2 (experiment 1) or 4 (experiment 2) male rats; after 4 hours, [3H]-thymidine (sp. act. 20 mCi/mM, approximately 500 µCi/kg) was injected --animals sacrificed after an additional 4 hours (8 hours post-treatment) and the DNA extracted from the bladders; sp. act. of DNA of individual rats determined; no details of methods and results reported as ratio of sp. act. of isolated DNA to mean sp. act. of controls (not defined whether received vehicle or nothing); negative for increased sp. act. after OPP but sp. act. increased 2-3 fold after SOPP; incomplete and, therefore, UNACCEPTABLE. (Gee, 3/30/87).
EPA memo [copy in document 129-048] dated March 22, 1982, reviewed the cellular regeneration test as: "The procedure adopted for demonstrating "cellular regeneration" appears to be adequate and the results acceptable. CDFA has no means of knowing whether EPA reviewed the identical documents on file at CDFA.

NEUROTOXICITY

Not required at this time.

The records shown below also are listed in the CDPR library computer printout of 7/5/91 for OPP (DPN 129) and OPP-Na (DPN 50438). Due to their trivial nature or due to the fact that they are partial or exact duplicates of other records in the Summary of Toxicology Data, these records have not been accorded a regular entry into the Summary of Toxicology Data. They are listed below in order to help the CDPR staff toxicologist verify that the Summary of Toxicology Data accounts for all records on file in the CDPR library.

Records: 004623, 035990, 035991, 050576, 060331, 060332, 096034